BRIEF REPORT

Penicillin Allergy Testing with Direct Oral Challenge in Primary Care

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Purpose: **Nearly 10% of the United States population has a reported penicillin allergy. However, many of these patients do not have true IgE-mediated allergy and are exposed to alternative antibiotics with increased risks of adverse outcomes, highlighting the importance of penicillin allergy testing. Patients with very low-risk penicillin allergies can safely undergo direct oral challenge (DOC) with a therapeutic dose of amoxicillin without prior skin testing. This study sought to establish a protocol for DOC in a primary care setting and test its efficacy and safety.**

Methods: **A standardized DOC protocol was developed at 2 primary care sites in Southeast Michigan. Forty-nine patients across the 2 sites were identified as having very low-risk penicillin allergies and underwent DOC. Follow up phone calls were completed 1 week and 6 months following DOC.**

Results: **All 49 patients had a negative DOC and successfully had their penicillin allergy delabeled from their electronic health record (EHR). No patients reported severe adverse reactions following DOC. All 22 patients who were successfully contacted 6 months after completing DOC reported willingness to take penicillin if prescribed in the future and believed they were no longer allergic to penicillin.**

Conclusions: **The results suggest that DOC may be effectively and safely implemented in a primary care setting to delabel penicillin allergies in patients with low-risk penicillin allergies. This study may serve as a model to increase access to DOC for adults in rural settings or low-income patient populations with limited access to allergy specialists. (J Am Board Fam Med 2024;37:991–995.)**

Keywords: **Allergy and Immunology, Electronic Health Records, Follow-Up Studies, Hypersensitivity, Michigan, Penicillin Allergy, Primary Health Care**

Introduction

Approximately 10% of patients in the US have a documented penicillin allergy, making it the most common antibiotic allergy.[1] However, over 90% of patients with a documented penicillin allergy do not have a type I IgE mediated hypersensitivity reaction when exposed to a penicillin.[2–3] Many documented penicillin allergies are based on remote unspecified reactions, mild cutaneous delayed hypersensitivity rashes, or family history of reaction alone.[2] Therefore, many patients with a history of documented penicillin allergy can tolerate penicillin. Delabeling of penicillin allergy traditionally requires recognition of potential mislabeling by a clinician and a subsequent visit to an allergist for skin testing and/or direct oral challenge (DOC).[1,4,5] As a result, delabeling of inaccurate penicillin allergy is infrequently done.[4] Inaccurate documentation of penicillin allergies is associated with increased use of broader spectrum antibiotics with greater side effect profiles, increased length of hospital stays, and increased risk for antibiotic-resistant infections, contributing to significant unnecessary health care costs and morbidity.[6–8] To reduce these risks, the Centers for Disease Control and Prevention (CDC) and other health care organizations have prioritized delabeling inappropriately labeled penicillin allergies.[9–10]

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Table 1. PEN-FAST Clinical Decision Rule Used in the Study

Criterion	Points
Five years or less since reaction	2
Anaphylaxis, angioedema, or severe cutaneous adverse reaction such as Stevens- Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	2
Treatment required for reaction	1
Points 0 = very low risk of positive penicillin allergy test; <1% 1 to 2 = low risk of positive penicillin allergy test; 5% 3 = moderate risk of positive penicillin allergy test; 20% 4 to 5 = high risk of positive penicillin allergy test; 50%	

Patients with very low-risk penicillin allergies can safely undergo either a single dose or graduated dose oral challenge without preceding skin testing, termed "direct oral challenge" (DOC).[2,11–13] In DOC, very low-risk patients receive oral amoxicillin in an observed medical setting and are delabeled from penicillin allergy if oral amoxicillin is tolerated both during and after a short period following the test. Patients are typically observed for 1 hour after the initial DOC to assess for immediate, or IgE-mediated hypersensitivity reactions which start within minutes to 1 hour after exposure and include urticaria, other cutaneous reactions, angioedema, hypotension, and anaphylaxis. Delayed hypersensitivity reactions can occur days to weeks after exposure and are usually mild cutaneous reactions, although rarely can be severe. However, in a large, randomized control trial of patients at low risk, the overall incidence of immediate and delayed hypersensitivity reactions to DOC was low, with fewer than 1% and approximately 5% of patients experiencing a mild immediate or delayed hypersensitivity reaction, respectively.[15] There is growing evidence that DOC may safely be completed in the primary care setting.[12–17]

Our study involved the implementation and evaluation of a DOC delabeling protocol for very low-risk penicillin allergy patients embedded within 2 different academic primary care sites. To our knowledge, this is the largest prospective study in the US evaluating DOC performed during a 1-on-1 visit with a Primary Care Physician (PCP) at the patient's primary care site.

Methods

Patients with documented penicillin allergy at 2 academic primary care sites underwent risk stratification

Table 2. Demographic Characteristics of Study Participants from January 2021-January 2023, Compared Between Two Academic Primary Care Sites. *P*-values from Fisher's Exact Test for Categorical Variables or 2-Sample T-test for Continuous Variables Comparing Site A to Site B. *$P < .05$

	Total (n = 49)	Site A (n = 30)	Site B (n = 19)	*P*-value
% of total count		61%	39%	
Median age as of 3/1/23 (IQR)	53 (29)	53.5 (27.8)	52 (29.5)	0.296
Sex				
Male (%)	26	20 (67%)	6 (32%)	0.021*
Female (%)	23	10 (33%)	13 (68%)	
Race				
White (%)	37	26 (87%)	11 (58%)	0.002*
Asian (%)	5	4 (13%)	1 (5%)	
African-American (%)	3	0 (0%)	3 (16%)	
Other (%)	4	0 (0%)	4 (21%)	
Ethnicity				
Hispanic (%)	4	0 (0%)	4 (21%)	0.018*
Non-Hispanic (%)	45	30 (100%)	15 (79%)	
Patients on medicaid or similar programs for low-income patients				
Yes	8	1	7	0.004*
No	41	29	12	
Other antibiotic allergies				
Yes	11	5	6	0.298
No	38	25	13	

Abbreviation: IQR, Interquartile range.

based on the PEN-FAST algorithm and exclusion criteria (Table 1). The PEN-FAST validated clinical decision rule allows for risk stratification for true IgE mediated penicillin allergy.[13] Patients are defined as at "very low-risk," or having a <1% chance of having a positive penicillin allergy test, if their reaction was cutaneous only, more than 5 years ago, was not characterized by anaphylaxis, angioedema, or severe cutaneous adverse reaction, and did not require treatment.[13] Penicillin-allergic patients with very low risk allergies (a score of zero on PEN-FAST) underwent outpatient oral challenge in our study. Patients with coinciding cephalosporin allergy were not excluded. Patients were contacted 1 week before testing to review the testing protocol, including antihistamine avoidance for 5 days before testing.

On the day of testing, staff who would potentially be involved in an emergency response to penicillin allergy were made aware of the appointment. After placing the patient in a room, inclusion and exclusion criteria were again reviewed. Patients were then given 1 dose of either oral amoxicillin 500 mg or amoxicillin/clavulanate 500/125 mg, if their prior reaction was to this formulation, and monitored over 60 minutes. Vitals were checked by a medical assistant on arrival and at the 30- and 60-minute timepoints. Patient rooms were in close proximity to nurse or medical assistant stations to allow easy reporting of symptom development. A red bag containing epinephrine, diphenhydramine, prednisone, and nebulized albuterol, either located in a red bag or nearby medication room, was readily accessible if needed during testing. Sixty minutes after the start of testing, the physician returned to the room and a β lactam allergy card stating the outcome and date of testing was provided to all patients. Delayed reaction precautions were reviewed with patients before checking out and emergency contact information provided. Patients' pharmacies were contacted to remove the allergy labels for patients with a negative direct oral challenge, as defined by the absence of an immune-mediated reaction during the DOC appointment. A follow-up phone call was completed after 1 week and again after 6 months. Patients unable to be contacted by phone on 3 separate occasions were excluded from survey results.

DOC visits were scheduled into 15 to 20-minute slots in the PCPs' regular schedules. Billing code 99213 with 95076 procedural charge was used for the encounter. The only staffing requirement for testing sessions, outside of the physician's time, was for a medical assistant to check vital signs. This study was reviewed and approved by the University of Michigan Institutional Review Board.

Results

From January 2021 to January 2023, 49 patients underwent DOC at the 2 sites. All 49 patients had a negative oral challenge and had their penicillin allergy removed from the Electronic Health Record (EHR). Thirty patients (61%) completed DOC at Site A with median age 53.5 (IQR 27.8) while 19 (39%) completed DOC at Site B with median age 52 (IQR 29.5) ($p_{age} = 0.296$). Patients at Sites A and B differed significantly with regards to sex, race, and ethnicity ($P = .021$, 0.002, 0.018, respectively), with Site B having a greater proportion of patients assigned female at birth or identifying as African American and/or Hispanic (Table 2). Eleven patients (22% of tested) had allergies to other antibiotics in addition to β lactams. Eight patients across sites

Table 3. Results of 1-Week and 6-Month Follow-up Survey Questions for Patients Who Underwent DOC Between January 2021 and January 2023 at Two Academic Primary Care Sites

Survey Questions		
1-Week follow up		n = 23/49 (RR = 47%)
Did you experience any rash, itching, or other adverse reaction in the past week that you believe is due to taking amoxicillin?	YES	0
	NO	23
Do you believe you are allergic to penicillin?	YES	2
	NO	21
Would you be willing to take penicillin if prescribed in the future?	YES	23
	NO	0
Do you think undergoing testing for penicillin allergy provides important information for your medical history?	YES	23
	NO	0
6-Month Follow Up		n = 22/49 (RR = 45%)
Have you taken a penicillin antibiotic since the oral challenge?	YES	0
	NO	22
Based on your answers to question 1, do you believe you are allergic to penicillin?	YES	0
	NO	22
Would you be willing to take penicillin if prescribed in the future?	YES	21
	NO	1

Abbreviation: RR, Response rate.

were covered by Medicaid or similar programs for low-income individuals.

Twenty-three patients (47%) were successfully contacted by phone 1 week following their DOC (Table 3). All stated they were willing to take penicillin if prescribed in the future and felt that undergoing penicillin allergy testing provided important information for their medical history. Two patients, both at Site A, felt they were still allergic to penicillin, citing prior delayed reactions to penicillin and questions regarding the reliability of DOC.

Twenty-two patients (45%) were successfully contacted by phone at the 6-month follow-up, including 14 (47%) from Site A and 8 (42%) from Site B ($P = .777$). No patients reported having taken a penicillin antibiotic since DOC. Twenty-one (95%) patients were willing to take penicillin if prescribed in the future and all 22 felt they were no longer allergic.

Discussion

In this study, we demonstrated that penicillin allergy testing with DOC was feasible in a primary care setting with respect to efficacy and safety. DOC resulted in the successful delabeling of 100% of patients who underwent testing, allowing for penicillin prescribing in the future if needed. In total, 21% of tested patients had additional antibiotic allergies; delabeling could potentially provide additional benefit in this subset. No patients who were available for a follow-up phone call experienced a rash, itching, or other adverse reaction during or in the week following DOC. Our observations regarding safety of DOC were similar to prior studies which reported a <5% rate of mild allergic reactions with no delayed reactions.[15–18]

Although no patients had used penicillin or a related antibiotic by the 6-month follow up, 95% continued to report willingness to take penicillin antibiotics in the future, indicating enduring patient confidence in negative direct oral challenge results. Patient trust in the results of DOC is especially important given variable perceptions regarding antibiotic reactions and the risk of using the respective antibiotics among patients and clinicians.[19] In addition, despite differences in patient demographics between the 2 clinic sites in our study, there were no significant differences across sites with regards to adverse reactions to DOC, patient-reported belief in continued allergy to penicillin, and willingness to take penicillin in the future suggesting safety and efficacy across diverse patient populations.

It should be noted that the DOC testing sessions in this study were generally easy to implement within the workflow of a busy outpatient clinic. Medical assistant staffing requirements were similar to that expected for the rooming of standard outpatient clinic visits. No extensive training was required for the physicians involved. A standard clinic "red bag" or emergency bag and the amoxicillin pill were the only supplies required for testing.

Limitations of our study include the small sample size and that approximately half of our patients were not successfully contacted by phone for follow-up after initial testing. Future studies incorporating longer follow-up would be helpful to ascertain future use of penicillin antibiotics following delabeling. Nevertheless, given limited access to specialty-trained allergists for penicillin allergy testing, particularly for rural and underinsured patient populations, our work may serve as a model for safely providing DOC in a primary care setting to adults and increasing access to this service for diverse patient populations.

To see this article online, please go to: http://jabfm.org/content/37/6/991.full.

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